

The Physiological Properties of Smooth
Muscle

by

Elizabeth Bacon Manuel

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Thesis

THE PHYSIOLOGICAL PROPERTIES OF SMOOTH MUSCLE

by

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INTRODUCTION

Smooth muscle is one of the fundamental tissues of the body. It is found in the digestive, respiratory, urinary, and genital tracts, in the walls of the arteries, veins, and larger lymphatics, and is scattered throughout the connective tissue of the skin, the capsule and trabeculae of the spleen, and the eye.

Although striated muscle is more differentiated and complex, the physiological properties of smooth muscle have been surrounded by more controversy and unsatisfactory assumptions. "In view of the importance of smooth muscle for many physiological functions, it seems unfortunate that widely different views have been expressed even on the most fundamental characteristics of this type of muscle. Its study has been difficult because of the complicated anatomical distribution and the frequent occurrence of spontaneous activity" (Bozler, 1939). Recently, through the use of new methods, a more satisfactory knowledge of the properties of smooth muscle has been gained. The purpose of this paper is to present a summary of the more recent findings concerning this subject.

MORPHOLOGY

The structure of the smooth muscle cell is very different from that of the other types. The cell is spindle-shaped with a single, oval nucleus located in the middle of the cell where the width is greatest. The nucleus is embedded in a granular, undifferentiated cytoplasm and contains several nucleoli and a clear basic chromatin network. In cross-section the cells are round or prismatic. The size of the fibers varies according to its environment. The largest ones are found in the pregnant uterus, and the smallest, in the blood vessels. The fibers are bound together by a dense network of reticular and elastic connective tissue. The reticular fibers branch and form a sheath around the cells. The force of the contracting muscle is exerted at the sides and is uniformly transmitted to these surrounding parts (Tiegs, 1924).

The external protoplasm is condensed but there is no true cell membrane as is found in striated muscle. Tiegs (1924) worked on the frog's stomach and the pregnant mammalian uterus, fixed in Bouin's solution and stained with iron haematoxylin. He reported the presence of a delicate homogenous membrane at the surface of the cell.

MYOFIBRILS. Because of the small size of the individual cells (15-500 microns in length and 2-20 microns in diameter as compared with a length of 1000-45,000 microns and a diameter of 10-150 microns for striated muscle) certain histological phases of the structure of smooth muscle have not yet been

satisfactorily determined. The first of these questions concerns the presence or absence of a contractile mechanism in the cytoplasm. In Tiegs' preparation (1924) myofibrils are seen as parallel threads running the length of the cell. Because of the presence of the large nucleus in the center of the cell, the fibrils must be confined to the periphery of the cell, thus leaving a clear area of sarcoplasm around the nucleus. In this area the chemical changes which produce contraction or relaxation may occur (Tiegs, 1924). The bounding fibrils of Heidenhain are coarser and thicker than the internal ones. Boeke (1932) states that the boundary fibrils are composed of longitudinal rows of dots which give the appearance of fibrils because of their close arrangement in rows and because they seem to be connected by fine threads of protoplasm. It is interesting to note that in preparations of frog's stomach and mammalian uterus stained with iron haematoxylin Tiegs (1924) describes the fibrils as having ill-defined, irregularly arranged transverse striations. There is also some doubt as to whether the fibrils converge and terminate at the ends of each cell or whether they continue in their parallel arrangement and pass through a series of cells.

In support of the presence of the myofibrils, Tiegs (1924) presents the following arguments:

1. The fibrils have the same index of refraction as the cytoplasm in which they are imbedded and therefore, they are not seen in unstained preparations.
2. The fibrils cannot be artifacts produced by coagulation

caused by the fixative since the fibrils are larger in preparations of the pregnant uterus than in preparations of the non-pregnant uterus. There appears to be no reason for larger coagula in the pregnant uterus.

3. In regions of contraction the fibrils are thicker. Unless the fibrils are present as a contractile mechanism, this fact seems hard to explain.

SYNCITIAL ARRANGEMENT OF FIBERS. Another point in question concerns the syncitial arrangement of smooth muscle fibers. Because of the small size of the fibers histological methods to determine a syncitial connection are not satisfactory. Smooth muscle is very difficult to tease apart. This fact is attributed to the presence of intercellular protoplasmic bridges, although the presence of these bridges is not certain. McGill (1909), working on the formation of smooth muscle, reported the presence of protoplasmic bridges as remnants of the embryonic state. On the basis of the response to electrical stimuli Bozler (1939) has proposed a syncitial arrangement for the uterus. The evidence advanced by Bozler in support of this theory will be presented later in the discussion of visceral smooth muscle. Cannon (1933) has found no evidence of a syncytium in the nictitating membrane. Fulton & Lutz (1942) have suggested a syncitial arrangement for the smooth muscle cells found in the walls of small blood vessels. In a preparation of the frog's retrolingual membrane which was cocaineized in order to render the nerve plexus non-functional, they found a non-nervous conduction mechanism which was syncytium-like in character.

INNERVATION

Smooth muscle is innervated from the autonomic nervous system. "The most general descriptive statement which can be made regarding the service of the autonomic system is that its prime function is the maintenance of stability or homeostasis in the fluid matrix of the organism" (Cannon & Rosenblueth, 1937)

ORGANIZATION OF THE AUTONOMIC SYSTEM. The autonomic system is composed entirely of efferent fibers which are distributed to the effectors through interposed peripheral neurones. In the cranial and sacral divisions, (parasympathetic) the pre-ganglionic fibers have a more or less scattered distribution; and the ganglia are found in or near the effector organs. The pre-ganglionic fibers of the thoracolumbar division (sympathetic) are collected in a chain of vertebral ganglia lying on either side of the midline of the dorsal body wall. The vertebral ganglia are interconnected by fibers from the spinal cord. From the vertebral ganglia fibers are distributed to sweat glands, and to the smooth muscle of the peripheral blood vessels and hair follicles. Other vertebral ganglia send out fibers which unite in the large unpaired prevertebral ganglia, (the coeliac and the superior and inferior mesenteric ganglia). From these ganglia postganglionic fibers are sent to the glands and smooth muscle of the abdominal viscera. By this arrangement the sympathetic division, with interconnecting fibers in the chain of vertebral ganglia and a union of fibers in the prevertebral ganglia, is organized for a diffuse distribution of nerve impulses, by which it is enabled to act as a unit. On the other

hand, the parasympathetic division is arranged for specific responses in separate organs, (Cannon & Rosenblueth, 1937).

DISTRIBUTION OF AUTONOMIC FIBERS TO SMOOTH MUSCLE. As a general rule each organ is innervated from both the sympathetic and parasympathetic systems; and the two systems have opposite effects. For example, the vagus has an inhibitory affect on the heart which is stimulated by sympathetic fibers. A given nerve may contain fibers which react differently on the effector; e.g. the vagus nerve inhibits the heart and stimulates the stomach (Cannon & Rosenblueth, 1937).

Following is a list of the organs containing smooth muscle and their nerve supply (Kuntz, 1934).

1. The blood vessels. Smooth muscle is found in the middle layer or tunica media of the walls of the arteries and veins. As the arteries branch into capillaries the muscle fibers cease to form a complete layer. On the capillary wall near the origin Rouget cells, which are considered to be modified smooth muscle cells (Bensley & Vimtrup, 1928), are found. The autonomic nerve supply to the blood vessels also contains afferent fibers which are components of the cerebrospinal nerve roots. The efferent fibers include both vasoconstrictor and vasodilator fibers. The former are sympathetic and the latter parasympathetic. The large blood vessels of the trunk are supplied by the nerves nearest them. The vessels in the head and neck are innervated from the cervical sympathetic ganglia. The arteries of the appendages receive their nerve supply mainly

through branches of nerves lying near them. The nerve supply to the veins has not been studied as completely as that to the arteries. The general plan of distribution for the arteries also holds for the veins. The nerve fibers terminate in plexuses in the adventitial and medial layers of the vessel walls. The end organs of the larger vessels are of two types: first, naked terminations consisting of bulb-like enlargements, brush or tree-like endings, and loops; and second, encapsulated end organs.

Not all the capillaries are directly innervated. Clark (1929), Penfield (1932), and Stohr, Jr. (1926), have been unable to find a nerve supply to the capillaries in the brain and spinal cord. The arrangement of the capillary nerve fibers is very complex. The fibers are derived partly from plexuses on the arteries from which the capillaries originate, and partly from nerves which are found in adjacent tissue. The fibers run along beside the capillaries coming into direct contact with them only at certain points. Each capillary is not always accompanied by a nerve fiber along its entire length.

2. The respiratory tract. Small amounts of smooth muscle are found in the lower part of the trachea where the cartilaginous rings are incomplete. In the bronchioles the amount of smooth muscle is increased. A few scattered muscle cells are present in the walls of the alveolar ducts and almost none in the alveoli (Cowdry, 1938). The larynx and trachea are innervated mainly from the superior cervical ganglia and from lar-

yngeal branches of the vagi. The bronchi and lungs are supplied through the pulmonary plexus which contains both sympathetic and vagus components..

3. The digestive tract. The smooth muscle is found in the digestive tract from the lower part of the oesophagus to the anus. It occurs in the tunica mucosa as a thin layer and in the tunica muscularis as the inner circular and outer longitudinal layers separated by the myenteric or Auerbach's plexus. The sympathetic supply to the pharynx is derived from the superior cervical ganglion; the parasympathetic from the glossopharyngeal and vagus nerves. Where the fibers from these two nerves meet they form the pharyngeal plexus. The oesophagus is supplied from the inferior cervical ganglion. Sympathetic fibers also reach the oesophagus from the stellate ganglia and the greater splanchnic nerve. The vagus nerve also sends branches to the oesophagus. The vagus fibers from the oesophageal plexus extend down to the stomach. The sympathetic supply to the stomach and small intestine is derived from the coeliac plexus. The small intestine receives fibers from the superior mesenteric plexus. The vagus nerves innervate the small intestine after leaving the coeliac plexus. The caecum, vermiform appendix, ascending, and transverse portions of the colon are supplied by the superior mesenteric plexus which contains both sympathetic and vagus fibers.. The descending colon and upper part of the rectum are innervated through the inferior mesenteric plexus.. The lower part of the rectum is supplied from the sacral division of the

parasympathetic system and from the inferior mesenteric plexus.

4. The sweat glands. The sweat glands are innervated from sympathetic fibers arising from the ganglia in the vertebral chain.

5. The spleen. Smooth muscle is present in the capsule and the trabeculae of the spleen. Cannon & Rosenblueth (1937) report only a sympathetic innervation for the spleen involving the greater splanchnic and phrenic nerves.

6. The urinary organs. The ureter is provided with an inner longitudinal layer of scattered muscle fibers and an outer continuous circular layer. The muscular layer of the bladder consists of a thick circular layer bounded on either side by a thin longitudinal layer. The ureter is supplied by the renal and hypogastric plexuses and by branches from the vagus. The bladder is innervated through the inferior mesenteric plexus and through the second and third sacral nerves which are incorporated in the vesical plexus.

7. The sex organs. Smooth muscle is found in the sperm ducts, the oviducts, the uterus, and the vagina. The parasympathetic nerve supply is derived from the sacral division. The sympathetic supply originates from the inferior mesenteric ganglia. Branches from both these regions unite to form an abundant innervation.

8. The eye. The smooth muscle of the eye is found in the nictitating membrane, the iris, and the ciliary muscles. The autonomic fibers reach the eye by way of the ciliary nerves. The sympathetic fibers are derived from the superior cervical ganglia. These fibers arise from the upper thoracic segments of the spinal

cord. The parasympathetic fibers arise in the ciliary ganglia from fibers which traverse the oculomotor nerve. The nictitating membrane of the cat is innervated only by sympathetic fibers (Cannon & Rosenblueth, 1937).

From the preceding list it can be seen that while the majority of the organs receive a double nerve supply, there are a few (namely, the spleen, sweat glands, nictitating membrane of the cat) which are innervated only by sympathetic fibers.

NERVE ENDINGS. A question of great importance, which is yet undetermined, concerns the end formation of the autonomic nerves in smooth muscle. Boeke (1940) describes "a system of very delicate interwoven and anastomosing non-myelinated nerve fibers". The delicate neurofibrillae form the terminations for the sympathetic plexus. The system is found everywhere in smooth muscle tissue and is especially abundant in the muscular coats of blood vessels and on the walls of capillaries. On the basis of histological work on the frog's stomach and the mammalian uterus fixed in Bouin's solution and stained with iron haematoxylin, Tiegs (1924) states that the nerve fibers enter the cell and terminate near the nucleus. He describes two fine reticula, a large one which is wound around the nucleus, and a smaller one which terminates in the granular substance near the nucleus. Eccles (1937) states that even though the nerve fiber penetrates the effector cell, there is no evidence for a continuity of the respective protoplasms.

Another open question concerns the number of cells which are innervated. Boeke (1932) found such a numerous arrangement of nerve fibers in the ciliary muscle of the eye, that he concluded every fiber might have an individual innervation. In other organs only a meagre innervation was found. Stohr, in 1931, concluded that only one in a hundred cells receives a nerve ending. In spite of the fact that several workers (Boeke, 1921, Tiegs, 1924) have reported two nerve filaments ending in a single cell, the source of the fibers has not been determined. As yet there is no histological evidence to prove that fibers from both divisions of the autonomic system terminate in a single cell. Therefore, it must be assumed that sympathetic fibers are supplied to some cells; and parasympathetic, to others (Cannon & Rosenblueth, 1937).

DIVISION OF SMOOTH MUSCLE

Bozler has suggested a division of smooth muscle into two types based on the histological structure and the reaction to stimuli.

1. The first type is visceral smooth muscle. Examples are the smooth muscle of the intestine and uterus. A syncytium like that found in cardiac muscle is formed; and the fibers possess an automaticity which produces a rhythmic activity originating in the fibers.

2. The second division consists of multi-unit smooth muscle and is typified by the smooth muscle found in the walls of the blood vessels and in the nictitating membrane. This type is made up of small units, activated by true motor nerves. It is analogous to skeletal muscle. The evidence for the existence of true motor units in the smooth muscle of the blood vessels will be discussed presently.

Each of these types will be discussed separately.

VISCERAL SMOOTH MUSCLE.

SYNCYTIAL ARRANGEMENT. The coordinated activity of the visceral muscles which have a meagre innervation (Stohr, 1931) has been difficult to understand on the basis of a nerve-muscle reaction. As an explanation for this apparent inconsistency, Bozler has presented the concept of a syncytial arrangement of the muscle fibers, similar to that found in cardiac muscle, as the mechanism for conduction of impulses. Because of the small size of the fibers histological methods for the determination of the existence of the syncytium are not satisfactory. Bozler (1938) has presented the following evidence as proof of the syncytial arrangement:

1. The response to electrical stimulation is very simple and is similar to that of striated muscle. It originates at the cathode end of a group of fibers, such as the uterus which in this case acts as a single motor unit.
2. When leads are applied, one to an injured and the other to an uninjured portion, an injury potential arises which is too large to have arisen from units as small as the individual muscle fibers. The potential is small compared to that of skeletal muscle because of the large amount of connective tissue present in smooth muscle.
3. During the passage of a wave of contraction a brief action potential is produced like the spike potential of skeletal muscle and nerve.

In all three cases the muscle has reacted as a single unit,

not as a mass of individual fibers. The responses are like those of striated muscle and nerve, and they differ from them only by their slower time characteristics.

McGill (1909) states that the smooth muscle of the alimentary tract is developed from a mesenchymatous syncytium surrounding the embryonic entoderm. She suggests that a syncytial structure is retained in the adult as a remnant of the embryonic state.

As opposed to the idea of a syncytium, the theory of Cannon & Rosenblueth concerning a transmitting substance might be mentioned briefly, as it will be discussed more fully in the section on chemical mediation. Cannon & Rosenblueth (1937) propose that the conduction in smooth muscle is effected by a chemical substance which is liberated when certain key cells are stimulated and which is spread to adjacent cells. Therefore, a syncytial arrangement of fibers and an abundant nerve supply are not necessary.

SPONTANEOUS CONTRACTIONS. A great deal of work has been done on the spontaneous contractions of visceral smooth muscle to determine whether the contractions are nervous or muscular in origin. Tiegs (1925) describes a nerve network in the longitudinal layer of smooth muscle in the stomach in which he believes the contractions originate. Since he denies the presence of intercellular protoplasmic connections (1924), he concludes that the nerve network acts as a conduction mechanism.

Eozler (1941) cites the observations of Alvarez & Mahoney

(1922) on intestinal contractions when the peripheral nerves were narcotized, and of Gasser (1926) on the spontaneous beating of nerve-free fragments.. From these observations and from his own work on the ganglion-free uterus, Bozler concludes that the contractions are myogenic and the result of the activity of many fibers coordinated by the syncitial arrangement of fibers.. Boeke (1940) denies that the supposedly nerve-free tissues are without nervous elements.. Ganglion-free strips of the circular muscle of the cat's intestine were found to be susceptible to drug action and electrical stimulation.. Neurofibrillar strands, whose nuclei are the so-called interstitial cells, were found to be scattered throughout the entire muscular layer. He declares that it is impossible to separate them from the muscle tissue.. Boeke, therefore, has concluded that the contractions are not undeniably of myogenic origin.

Bozler (1941) has found that the fundamental process underlying the spontaneous contractions of the intestine is a discharge of impulses conducted within the muscle.. That no nervous element is employed in the conduction of impulses is evident from the fact that cocaine, which ordinarily blocks the myoneural junction, has no effect except in very high concentrations (Bozler, 1939).. In cocainized preparations of the frog's retro-lingual membrane lack of response of the small blood vessels to stimulation of the nerves shows that the nerve plexus is non-functional. Direct stimulation of the blood vessel wall produces a constriction of the exact area which responded to stim-

ulation of the nerve in an uncocainized preparation. The limited response is evidence of a non-nervous conduction mechanism like a syncytium. Vascular smooth muscle may also have a syncytial arrangement like that proposed for visceral smooth muscle. (Fulton & Lutz, 1942).

The spontaneous contractions of the intestine and uterus are preceded and initiated by a local potential, recognizable as a weak activity at the site of the pacemaker (Bozler, 1942). The local potential is interpreted as a change in the polarization of the cell surface. It is the basis for the automaticity of smooth muscle. The spontaneous tendency of the cell surface to depolarize can be found in all regions of the muscle, not just at the point where the impulses originate. Adrenalin, which decreases the excitability of intestinal and uterine smooth muscle, does not affect the local potentials which can take place while no impulses are discharged. This fact is offered as further proof that inhibition in smooth muscle is the result of a decrease in excitability, not of a decrease in the stimulus for the discharge of impulses (Bozler, 1942).

The electrical changes accompanying the spontaneous contractions of many smooth muscles have been recorded in order to determine the relationship between the electrical deviations and the mechanical cycles (Cannon & Rosenblueth, 1937). The intestine, stomach, and ureter show a one-to-one ratio which is interpreted as signifying rhythmic twitches. A ratio of several action potentials to one contraction was found in the re-

tractor penis and uterus. This ratio denotes a state of tetanus. Bozler (1941) has concluded that the burst or discharge of impulses may be fused into a continuous state of electrical negativity, and so, may produce a movement analagous to a tetanic contraction in skeletal muscle..

An interesting study on the varying rates of contraction of the rabbit's intestine was conducted by Alvarez (1914). The experiments were performed on strips of intestine removed from anesthetized rabbits and kept at 37°C. It was found that the rhythm of the intestine varied inversely as the distance from the pylorus. The upper and lower parts of the intestine react differently to adrenalin. The inhibition is greater and the recovery time is longer at the lower end. The amplitude, indicating a difference in tone, is less in the duodenal region than in the ileum. The greater tone and irritability and the faster rhythm of the duodenum are associated with the more rapid peristalsis of this region.

EXCITABILITY. It has been questioned whether smooth muscle is electrically excitable (Bozler, 1939). An electrical stimulus applied to an innervated muscle may stimulate the nerves which in turn activate the muscle. For this reason the response of a muscle to direct stimulation does not mean that the effector is electrically excitable (Cannon & Rosenblueth, 1937). Any muscle may be expected to contract in response to a direct stimulation. A muscle which reacts to nerve stimulation by relaxation should also contract with direct stimu-

lation. Cannon & Rosenblueth (1937) concluded that the uterus of the cat, which has only an inhibitory nerve supply, is electrically inexcitable since it responded by relaxation to a direct stimulation. They also found that the responses of a denervated nictitating membrane, which contains no nerve cells, differ from those of innervated muscles to nerve impulses. Changes in the intensity and frequency of the stimuli produced no spatial and temporal variations. The response to an electrical stimulation is small as compared with the response to adrenalin (Rosenblueth, 1941). From these reactions Cannon & Rosenblueth have concluded that smooth muscle is electrically inexcitable. They assume that the response to an electric current is due to stimulation of the nerve fibers in the muscle, or to the injurious effects of the current. Bozler (1939) found that the uterus (during estrus only) can be stimulated by direct electric shocks. As an explanation for the difficulty in stimulating the nictitating membrane, he cites the anatomical work of Acheson (1938) who found that the movements of the membrane are controlled by a muscle which lies in the peribulbar fascia and extends but slightly into the membrane. Bozler (1939) proposes that only a small part of the electric current will pass through the muscle fibers because of their short length. Therefore, the threshold is high which accounts for the difficulty in direct stimulation. The responses of smooth muscle vary with the physiological condition of the tissue. In a condition of low excitability only those fibers with a low threshold will respond with the result

that the conduction of impulses may be blocked (Bozler, 1941).

EFFECTS OF ELECTRICAL STIMULATION. Cannon & Rosenblueth (1937) have divided smooth muscle into two types according to the type of response to single shocks. The first type (single-volley) includes the smooth muscle of the nictitating membrane, the pilomotor muscle, and the bladder. It responds with a typical twitch to a single shock applied to the excitatory nerve supply. This type will be more fully discussed in the section on multi-unit smooth muscle. The second type (multiple-volley) must be stimulated with repetitive shocks in order to elicit a response. The smooth muscle of the uterus is included in this type. From the electromyograms, it is seen that in the response of the single-volley type to nerve stimulation there are three components, of which only the second and third occur in the multiple-volley type. The multiple-volley type of response is characterized by a long period of latency. According to Cannon & Rosenblueth the second component is indicative of the depolarization of the cells adjacent to the ones stimulated, and the penetration of the chemical mediator. The third component is inseparable from the mechanical response of contraction.

Electrical stimulation of a sympathetic nerve or the application of adrenalin diminishes or stops the spontaneous activity of some organs, for example, the uterus, stomach, and intestine. Bozler (1940), in work on the uterus of the cat during estrus (the only time it is electrically excitable) found that the response to stimulation of the hypogastric nerve is diphasic,

contraction followed by relaxation. Formerly, it was thought that the hypogastric nerve contained both excitatory and inhibitory fibers. Bozler has concluded that both reactions are really phases of the same response. The sympathetic nerves initiate muscular impulses and also, lower the excitability. Nerve stimulation or adrenine first increases muscular activity; and then, when the excitability drops below a certain level during continuous stimulation, the discharge of muscular impulse is blocked. If the block occurs rapidly the excitatory phase may be masked. Bozler found the characteristic diphasic response in the urinary bladder and the stomach, also.

In 1941 Bozler conducted experiments on the uterine muscle of the cat and the guinea pig in order to determine the mechanical properties of resting smooth muscle.. He found that the lengthening of a resting strip of muscle under a constant load, and the lengthening of the muscle after contraction, follow the same time course. Similar results were found by Bozler for the gradual distention of perfused blood vessels under an increased pressure, and the relaxation following contraction. These observations suggest that the relaxation of smooth muscle is purely a physical process and is controlled by the same viscous forces which control passive distention.

EFFECTS OF ANOXIA. Epinephrine and ephedrine have similar actions, although the latter has a more sustained effect.. It has been proposed that the effect of these compounds is brought about in two ways (Van Liere, Lough, & Sleeth, 1936).

First, ephedrine stimulates the sympathetic splanchnic nerves to the stomach. These fibers have an inhibitory action on the gastric musculature. Second, ephedrine may relax the smooth muscle directly. As might be expected ephedrine has been shown to delay the gastric emptying time (Van Liere, Lough, & Sleeth, 1936).. The production of epinephrine during anoxemia is one of the factors in the inhibition of gastric motility at reduced pressure of oxygen (Van Liere, 1936). Another mechanism is the effect of anoxemia on the pyloric sphincter.. Anoxemia causes a vagospasm which appears as a pylorospasm until a critical threshold is reached. After this point the tone of the gastric musculature is decreased with a subsequent depression of the motility (Van Liere, Crisler, & Wiles, 1935). The same mechanism is involved in cases of acute hemorrhage, that is, loss of blood causes an anoxia (Van Liere, Sleeth, & Northrup, 1936).

MULTI-UNIT SMOOTH MUSCLE

DIVISION INTO MOTOR UNITS. According to the classification of smooth muscle proposed by Bozler and followed by this paper, multi-unit smooth muscle includes the type found in the walls of the blood vessels and in the nictitating membrane. The muscle fibers are grouped into small units similar to the motor units found in skeletal muscle, and are activated by true motor nerves (Bozler, 1939). The theory of true motor units in this type of smooth muscle is not accepted by all workers. Klopp (1940) found that when some of the postganglionic fibers to the nictitating membrane were cut only localized areas responded to epinephrine or electrical stimulation. This would indicate a division into units.. Klopp also found that the response was increased with an increase in the frequency of stimulation.. He concluded that any division into units was merely relative and that the number of fibers controlled by a given nerve was variable.. Rosenblueth has denied the existence of motor units and argues instead for a system of chemical mediation whereby a larger amount of the transmitter is liberated with a greater frequency of stimulation. A spatially limited vascular response to stimulation of the nerves of the retrolingual membrane of the frog indicates an arrangement of the muscle fibers in motor units (Fulton & Lutz). Fulton & Lutz (1942) have suggested a syncytial arrangement for the vascular smooth muscle.. They found in cocaine preparations that stimulation of the blood vessel wall produced a response confined to the exact area as in

the innervated preparation.

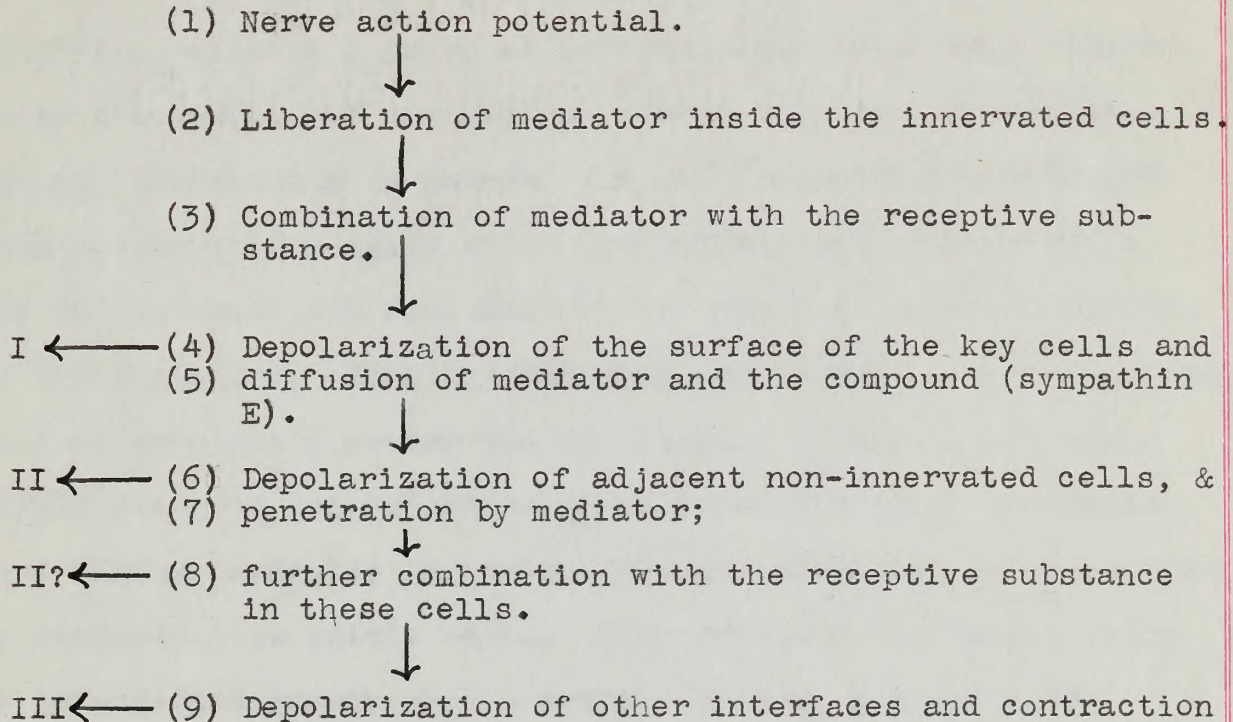
EFFECTS OF ELECTRICAL STIMULATION. Multi-unit smooth muscle is included in the type designated by Cannon & Rosenblueth (1937) as single-volley since it responds with typical twitches when single shocks are applied to the nervous supply. The response to a single shock is very complex. Three components have been distinguished. The polarity of the components depends upon the orientation of the muscle cells with respect to the electrodes.. The first component is a monophasic spike preceding contraction. The magnitude of the first component varies directly as the number of active muscle cells between the recording leads.. With repetitive stimulation the first component declines as the frequency is increased. The spike potential in skeletal muscle is "the electric index of a transmitted wave of depolarization responsible for conduction of the excitatory process in the muscle". (Cannon & Rosenblueth 1937). Because of the small size of the fibers, conduction is not indispensable in smooth muscle as it is in skeletal muscle; and response of a muscle to nerve activation may occur without a spike potential. From this evidence it is postulated that the first component is probably not analagous to the spike potential of skeletal muscle. The first component might be correlated with production of the chemical mediator which is liberated between the nerve action potential and the mechanical response; or the change produced by the mediator.. The first component declines during repetitive stimulation because of the accumula-

tion of the mediator from previous shocks in such an amount that it maintains the cell surfaces depolarized throughout the period of stimulation.. The second component is polyphasic and is even more complex and variable than the first. The point of inception of the second component is difficult to determine, since the first merges completely into it.. The third component is a prolonged monophasic deviation, inseparable from the contraction itself. The beginning of the the third component is also difficult to determine. Both the second and the third component are capable of summation with repeated stimulation at high frequencies. The significance of the second component is obscure; but it is probably the depolarization of adjacent cells and the further diffusion of the mediator.. The third component is inseparable from the mechanical response of the muscle.

When the nictitating membrane contracts with the application of adrenalin the only component in the response is the third. The reason for this may be that adrenalin partly or wholly depolarizes the cells. Therefore, the first component is decreased since its magnitude depends upon the degree of depolarization of the cell surface.

Following is a summary (Cannon & Rosenblueth, 1937) of the steps by which the nerve impulse is transferred into a mechanical response.. The electric components, as shown on the electromyograms, may not be indispensable steps in the chain; since it has been questioned whether smooth muscle is

electrically excitable.



Although multi-unit smooth muscle may be grouped into motor units, the units are not as rigid as those of striated muscle. With an increase in stimulation, there is a corresponding increase in the response of the muscle. The all-or-none principle cannot be applied to the smooth muscle of the nictitating membrane (Cannon & Rosenblueth, 1937)

NEURO-MOTOR MECHANISM OF THE SMALL BLOOD VESSELS. The walls of the arterioles and venules are made up of three coats; a layer of connective tissue fibers, several layers of smooth muscle, and an inner layer of endothelial cells. As the arter-

ioles branch into capillaries the outer coat disappears; and the muscle fibers cease to form a complete layer. Surrounding the capillary walls is a group of pericapillary cells or pericytes. These are usually of connective tissue origin and therefore, are not contractile in nature. In 1873 Rouget discovered certain pericapillary cells which are contractile. These cells lie on the capillary wall with their long axes parallel to that of the capillary. Each one has many processes which extend more or less completely around the capillary. Bensley & Vimtrup (1928) describe the Rouget cells as differing from the connective tissue pericytes in possessing myofibrils and in being able to contract like muscle cells. They consider the Rouget cells to be modified smooth muscle cells. Vimtrup & Krogh (1929) describe a series of transitional forms between the uniform layer of muscle cells of the arterioles and the branched Rouget cells on the capillaries. The modified smooth muscle cells of the capillaries are confined to their origins.

Rouget cells are not found on all capillaries, but when they are present they take part in the contractile process, (Krogh, 1929). A network of nerve fibers is found in conjunction with the capillary network. The nerve fibers make actual contacts with the capillary wall at certain points. Knoblike terminal enlargements have also been described on the capillaries. The capillary circulation is controlled without the aid of the supplying vessel (McDowall, 1935; Jones, 1936; Fulton & Lutz, 1940). The modified smooth muscle cells of the capillaries are

confined to the capillary origin. Fulton & Lutz (1940) have demonstrated a mechanism for capillary control in the frog. The vaso-motor nerves supplying the modified smooth muscle cells contain both dilator and constrictor fibers.. Faradic stimulation of these nerves produces a diphasic response, dilation followed by constriction, which extends no farther than the region of the capillary origin. This region acts as a sphincter to control the blood flow independently of the supplying vessels.

CHEMICAL MEDIATION

"Nervous impulses must not only be conducted along nerve fibers but must also jump the gap between neurons, or from neuron to effector cell" (Evans, 1939). There are two theories concerning the mechanism of transmission across the gap or synapse, the electrical or action-current hypothesis, and the chemical mediation theory. The latter theory had been merely suggested by early workers, until in 1921, Loewi established the existence of the chemical agencies. He stimulated the cardiac branch of the vagus nerve supplying a frog's heart filled with Ringer's solution, and found that the solution then had the power to induce the typical inhibitory responses in another heart. Stimulation of the sympathetic nerve gave the opposite effect.

The phenomenon of chemical mediation must be inferred since no one has seen the process. The conclusion is that whenever an autonomic nerve is stimulated, it liberates a chemical deputy which produces the results on the cells formerly attributed to the nerve impulse alone. The evidence for the liberation of a chemical mediator upon stimulation of the parasympathetic branch of the autonomic nervous system is given below (Brown, 1937).

(1) An unstable ester of choline is liberated when the vagi are stimulated.

(2) This substance reproduces the effect of nerve

stimulation.

(3) The action on the heart is prevented by atropine.

(4) In the presence of atropine stimulation of the vagus liberates acetylcholine; but it is ineffective.

(5) The heart, blood, and other tissues contain an enzyme, (choline esterase) which hydrolyses acetylcholine.

(6) This enzyme is inhibited by eserine which prolongs and intensifies the nerve stimulation.

Eccles (1937) has taken an intermediate position, and has suggested that both chemical and electrical transmitters may be compatible. Two main categories are proposed: First, transmitters of long duration, an example of which is the action of the vagus on the heart, whose action is performed by liberation of chemical substances. Second, transmitters of short duration which may be electrical or chemical. The necessarily rapid disappearance of acetylcholine at the ganglionic synapses is one of the chief objections to the chemical hypothesis, since it is apparent that there is not enough cholinesterase in the ganglion to accomplish the rapid hydrolysis.

Fulton & Lutz (1942) have found that blood vessels do not influence adjacent ones of another motor unit, as would be the case if a chemical mediator were liberated when the nerve was stimulated. Because of the abundant nerve plexus found in vascular smooth muscle they conclude that a diffusion of chemical substances is not necessary.

THE SYMPATHOMIMETIC SUBSTANCE. When the sympathetic nerve supply to a wide range of organs, liver, heart, intestine, uterus, bladder, pilomotor muscles of the cat's tail, iris, ciliary body, and the salivary glands, is stimulated a substance resembling adrenine is released. This substance is called sympathin, and is capable of mimicking the action of the sympathetic system in other organs.. Sympathin may be secreted from the nerve terminations or from the affected cells, it is not clear which (Rosenblueth, 1937). In natural conditions sympathin is released as a result of excitement, cold, asphyxia, and hypoglycemia. Unlike acetylcholine which is rapidly destroyed, sympathin diffuses into the blood stream and is carried to other parts of the body. Sympathetic impulses produce enough of the mediator for local direct action and also for remote responses. Sympathin is reinforced by adrenine which is found simultaneously circulating in the blood (Cannon & Rosenblueth, 1937).

The sympathetic system is arranged to work as a unit and to bring about diffuse effects. This system is reinforced by the discharge of local and circulating sympathin and circulating adrenine, all of which work together to produce a unified response.

Sympathin has many of the properties of adrenine. Its influence on an organ is increased by a previous injection of cocaine; it is rendered ineffective when mixed with eosin and exposed to air for twenty-four hours or after being heated to

one hundred degrees, Adrenine and sympathin have a different effect on peripheral structures, e.g. both accelerate the heart but have opposite effects on the blood pressure. From other evidence it may be concluded that the sympathin liberated by stimulation of the cardiac, hepatic, lumbar, and hypogastric sympathetic fibers is different from adrenine; and that sympathins from different regions have different properties (Cannon, 1933). All these observations support the theory of the existence of two sympathins- E and I. E is liberated from the smooth muscle which contracts upon stimulation of the sympathetic nerves; and I from that inhibited.

Certain sympathetic effects seem to be parasympathetic, e.g. sweating can be induced in a cat by pilocarpine but not by adrenine, and by stimulation of the sympathetic nerves. In this case acetylcholine is liberated, not sympathin. Therefore, the two kinds of fibers in the sympathetic system are designated as cholinergic and adrenergic..

THE PARASYMPATHOMIMETIC SUBSTANCE. Acetylcholine is liberated when the parasympathetic supply to the heart, gastrointestinal tract, salivary glands, ciliary body, iris, bronchioles, and bladder is stimulated. Although cholinergic fibers have also been found in sympathetic nerves, there is as yet no conclusive evidence for the presence of adrenergic fibers in the parasympathetic division (Cannon & Rosenblueth, 1937). Acetylcholine is the only choline ester which has been isolated from animal tissue. It is not present in a free state in the tissues

since it is rapidly hydrolysed by the tissue esterase. The actions of choline esters can be divided into two groups: (1) the muscarine-like actions on the parasympathetic effectors, and (2) on the nicotine-like action as a transmitter at the ganglionic synapse and at the neuro-muscular junction of skeletal muscle (Brown, 1937).

The characteristics of the muscarine-like transmissions include the following:

- (1) A long latent period due mostly to muscular delay not to slowness of liberation of mediator.
- (2) A long local persistence of the transmitter.
- (3) Summation by the additive effects of the persisting transmitter.
- (4) The effects of diffusion in distant parts are not easily observable in the absence of eserine.
- (5) Eserine increases the magnitude and duration of the response
- (6) Paralysis by atropine.

In comparison the characteristics of the nicotine-like transmissions are:

- (1) The latent period in both the ganglionic synapse and the neuro-muscular junction is short.
- (2) The transmitter is destroyed during the refractory period of the effector.
- (3) Distant effects do not occur.

CONCLUSION.

From the points summarized in this paper it is evident that there are two types of smooth muscle which differ distinctly both in histological and physiological properties. Because of this fact each of the two types must be studied separately and assumptions based on evidence from one type can not be transferred to the other.

The division followed by this paper was proposed by Bozler. It separates smooth muscle into two types , multi-unit and visceral smooth muscle. The visceral fibers possess spontaneous rhythmic contractility, muscular in origin, although this fact has been questioned.. However, since a great deal of work has been done on the automatic activity of isolated preparations it does not seem possible that the contractions could be neurogenic. Because of the conduction brought about by the syncytial arrangement, and the relative length of these fibers as compared to those in the other group, the responses of visceral muscle as a group have certain characteristics in common with skeletal muscle..

Concerning multi-unit smooth muscle there is a controversy as to whether the innervation is carried out in small motor units or by stimulation of key cells and subsequent diffusion of a chemical mediator to adjacent cells. There is a graded response but that may be accounted for by a less rigid boundary of the motor unit than is found in striated muscle. That is, with an increase in stimulation more fibers may be affected by the nerve

impulse.

The control of smooth muscle is further complicated by the release of chemical mediators upon stimulation of the autonomic nerves. The mediators may act locally or may be carried in the blood. In either case the action is exerted on the effector cells.

The autonomic nervous system has been divided into adrenergic and cholinergic fibers, a grouping more in keeping with the functional aspects of the fibers.

Myofibrils have been seen in some preparations (Fulton, 1944) but these have been called merely artifacts as the result of degeneration during fixation. Because of the larger size of the fibrils in the present work than in the non-prepared, and because in regions of contraction the fibrils are thicker, these appear that they cannot be artifacts. The difficulty experienced in teasing smooth muscle apart is attributed to the presence of intercellular protoplasmic bridges. Evidence of a syncytial arrangement has been found in the uterus (Euler, 1939) and the smooth muscle in the walls of the small blood vessels (Fulton & Lutz, 1942); but not in the nictitating membrane (Cannon, 1933).

ABSTRACT

Although smooth muscle is one of the important tissues of the body, widely different views have been expressed on even its most fundamental characteristics. The study of smooth muscle has been complicated by its spontaneous activity, and double innervation. The purpose of this paper is to present some of the more recent findings concerning this subject.

The smooth muscle cell is a spindle-shaped fiber with a single, oval, centrally placed nucleus. The size of the fibers varies greatly according to their environment. The fibers are bound together by a dense connective tissue network. There is no true cell membrane as is found in striated muscle.

Myofibrils have been seen in some preparations (Tiegs, 1924) but these have been called merely artifacts as the result of coagulation during fixation. Because of the larger size of the fibrils in the pregnant uterus than in the non-pregnant, and because in regions of contraction the fibrils are thicker, Tiegs argues that they cannot be artifacts. The difficulty experienced in teasing smooth muscle apart is attributed to the presence of intercellular protoplasmic bridges. Evidences of a syncytial arrangement have been found in the uterus (Eozler, 1939) and the smooth muscle in the walls of the small blood vessels (Fulton & Lutz, 1942); but not in the nictitating membrane (Cannon, 1933).

Smooth muscle is innervated from the autonomic nervous system which is composed of efferent fibers distributed to the effector organs through interposed peripheral neurones. As a general rule each organ is innervated from both the sympathetic and parasympathetic systems; and the two systems have opposite effects.

The nerve endings may enter the cell and terminate near the nucleus (Tiegs, 1924), or closely adhere to the outside of the cell. The number of cells in a given tissue which are innervated is variable. In the ciliary muscle there is a numerous arrangement of nerve fibers (Boeke, 1932); and in the stomach only about one cell in every hundred is innervated (Stohr, 1931).

Bozler has suggested a division of smooth muscle into two types; First, visceral smooth muscle which is characterized by a syncitial arrangement of fibers. Examples are the muscle of the intestine and uterus. The second type is multi-unit smooth muscle and is found in the blood vessels and the nictitating membrane. It is composed of small units activated by motor nerves.

The coordinated activity of visceral smooth muscle is explained by the syncitial arrangement of fibers which affords a mechanism for the conduction of nervous impulses. Bozler (1941) has found that the spontaneous contractions characteristic of visceral smooth muscle are due to bursts of impulses conducted within the muscle. Cocainized preparations of the small blood vessels of the retrolingual membrane of the frog respond with

constriction to a direct stimulation. Since the area is the same as that which contracted in innervated preparation the conduction of the impulse must be myogenic (Fulton & Lutz, 1942). The electrical changes accompanying the spontaneous contractions have been recorded by Cannon & Rosenblueth (1937). They show a one-to-one ratio for the intestine, stomach, and ureter signifying rhythmic twitches. Other muscles, uterus and retractor penis, show a many-to-one relationship denoting a state of tetanus. According to Cannon & Rosenblueth (1937) smooth muscle is electrically unexcitable. The changes produced by stimulation are caused by activation of the nerve fibers in the muscle, or by the injurious effects of the current.

Anoxia causes an increase in gastric motility, first by the production of epinephrine which inhibits the stomach by stimulating the splanchnic nerves; and second, on a vagospastic pylorospastic basis up to a critical threshold when the tone of the musculature is decreased (Van Liere, et al., 1936).

The fibers of multi-unit smooth muscle are grouped into small units and are activated by motor nerves. The motor units are more variable in extent than those found in striated muscle. Fulton & Lutz (1942) have suggested a syncytial arrangement for vascular smooth muscle. The electrical response to single shocks has been recorded by Cannon & Rosenblueth (1937). The response is made up of three components which are interpreted as denoting the depolarization of the surface of key and adjacent cells and the diffusion of a chemical mediator.

The small blood vessels have contractility independent of the supplying vessels. The size of the capillary is controlled by innervated modified smooth muscle cells which act like a sphincter at the origin of the capillary.

Nervous impulses may be transmitted at the synapse by electrical or chemical mediation. Both theories have strong and weak points in their favor. When the sympathetic nerves are stimulated a substance resembling adrenaline is released. It diffuses into the blood stream and is carried to other parts of the body. The sympathetic system is arranged to work as a unit and to bring about diffuse effects. This system is reinforced by the discharge of local and circulating sympathin. There are two types of sympathin with different effects. Sympathin E is liberated from the smooth muscle which contracts upon stimulation of the sympathetic nerves; and I from that inhibited.

Acetylcholine is liberated when parasympathetic nerves are stimulated. In contrast to sympathin acetylcholine is very rapidly hydrolysed in the tissues.

It is evident from the points summarized in this paper that smooth muscle is composed of dissimilar groups with varying characteristics. Because of this fact each of the two types must be studied separately; and assumptions based on evidence from one type cannot be transferred to the other.

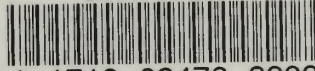
BIBLIOGRAPHY

- Alvarez, W. C. 1914 Functional Variations in Contractions of Different Parts of the Small Intestine.
Am. J. Physiol. 35:177
- Boeke, J. 1940 Problems of Nervous Anatomy. London.
- Bozler, E. 1939 Muscle. Ann. Rev. Physiol. v.1:217.
- Bozler, E. 1940 An Analysis of the Excitatory and Inhibitory Effects of Sympathetic Nerve Impulses and Adrenalin on Visceral Smooth Muscle. Am. J. Physiol. 130:627.
- Bozler, E. 1941 The Mechanical Properties of Resting Smooth Muscle. J. Cell. and Comp. Physiol. 18:385
- Bozler, E. 1941 Action Potentials and Conduction of Excitation in Muscle. Biol. Symp. v.3
- Bozler, E. 1942 The Activity of the Pacemaker Impulse Previous to the Discharge of a Muscular Impulse.
Am. J. Physiol. 136: 543
- Bozler, E. 1942 Action Potentials Accompanying Conducted Visceral Smooth Muscle. Am. J. Physiol. 136:553
- Brown, G. L. 1937 Transmission at Nerve Endings by Acetylcholine. Physiol. Rev. 17:485
- Cannon, W. B. 1933 Chemical Mediation of Autonomic Nerve Impulses. Science 78:43
- Cannon, W.B. & A. Rosenblueth. 1937 Autonomic Neuro-Effector Systems. New York.
- Cowdry, E.V. 1938 A Textbook of Histology. Philadelphia.
- Eccles, J. C. 1937 Synaptic & Neuro-Muscular Transmission. Physiol. Rev. 17:538
- Evans, C. L. 1926 The Physiology of Plain Muscle. Physiol. Rev. 6:358
- Evans, C. L. 1939 Recent Advances in Physiology. Sixth Edition Philadelphia.
- Fischer, E. 1943 Muscle. Ann. Rev. Physiol. v. 5:133
- Fulton, G. P. & B. R. Lutz. 1940 The Neuro Motor Mechanism

- of the Small Blood Vessels of the Frog. Science 92
- Fulton, G. P. & B. R. Lutz. 1942 Smooth Muscle Motor Units in Small Blood Vessels.. Am. J. Physiol. 135:531
- Jones, T. 1936 The Structure and Mode of Innervation of Capillary Blood Vessels. Am. J. Anat. 58:227
- Klopp, C. T. 1940 Reactions of Partially Denervated Smooth Muscle to Adrenalin and Sympathin. Am. J. Physiol.. 130:475
- Krogh, A. 1929 The Anatomy & Physiology of Capillaries. New Haven.
- Kuntz, A. 1934 The Autonomic Nervous System. Philadelphia.
- MacKay, M. E. 1930 The Action of Histamine on the Motility of Different Parts of the Intestinal Tract. Am. J. Physiol. 95:527
- McDowall, R.J.S.. 1935 The Nervous Control of the Blood Vessels. Phys. Rev. 15:98
- Morison, R.S. 1940 The Effects of Adrenalin and of Nerve Stimulation on the Mechanical and Electric Responses of Uterine Muscle. Am. J. Physiol. 128:372
- Rosenblueth, A.. 1937 The Transmission of Sympathetic Nerve Impulses. Physiol. Rev. 17:514.
- Rosenblueth, A. 1941 Conduction in Smooth Muscle. Biol. Symp. v. 3
- Stohr, P. 1931 Quoted by Boeke, 1940
- Tiegs, O. W. 1924 Studies on Plain Muscle. Austr. J. Exp. Biol. & Med. Sci. 1:131
- Tiegs, O. W. 1925 Nerve Net of Plain Muscle and its Relation to Autonomic Rhythm Movement Austr. J. Exp. Biol. & Med. Sci. 2:157
- Van Liere, E., G. Crisler, & I. A. Wiles. 1935 The Effect of Anoxemia on the Pyloric Sphincter. Am. J. Physiol. 111:330
- Van Liere, E., C. K. Sleeth, & D. Northrup. 1936 The Effect of Acute Hemorrhage on the Emptying Time of the Stomach Am. J. Physiol. 117:226

- Van Liere, E. 1936 Effect of Anoxemia on the Emptying Time
of the Human Stomach. Arch. Int. Med. 58:130
- Van Liere, E., D.H.Lough, & C.K.Sleeth 1936 The Effect
of Ephedrine on the Emptying Time of the Human Stomach
J. Am. Med. Assoc. 106:535
- Van Liere, E.. 1941. The Effect of Anoxia on the Alimentary
Tract. Physiol. Rev. 21:307
- Van Liere, E., & J. C. Stickney 1942 Acclimatization
to Low Oxygen Tensions in Relation to Gastric Emptying
Am. J. Physiol. 137:160
- Wiersma, C. A. G. 1941 The Efferent Innervation of Muscle.
Biol. Symp. v.3

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